

Reproductive Effects of Inorganic Borates on Male Employees: Birth Rate Assessment

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The purpose of this study was to investigate the potential for reproductive effects of inorganic borate compounds on male employees. The standardized birth ratio (SBR) methodology was used to assess fertility among male employees, using live births as the measured end point. The ratio of female to male births was also assessed. Data were collected via questionnaires and telephone follow-up interviews. Medical insurance records were assessed for nonresponders. Exposures were assessed using three semiquantitative categories. We found a statistically significant increase in fertility as measured by live births among the employees of the inorganic borate facility. There does not appear to be any decrease in fertility due to exposures either as analyzed by the borate exposure categories or over time, which is an indirect measure of exposures. We found a nonstatistically significant increase in the percentage of female offspring. This increase was due, not to a deficiency of male offspring, but rather to a marked increase in the numbers of female offspring. This increase in percentage female offspring does not appear to be related to exposures to inorganic borates. Based on the data, exposures to inorganic borates do not appear to adversely affect fertility in this population. — *Environ Health Perspect* 102(Suppl 7):129–131 (1994)

Key words: male reproduction, standardized birth ratio, sex ratios

Introduction

This study's purpose was to investigate the effects of exposure to inorganic borates on the reproductivity of male employees. This was not a study of developmental outcomes.

Other authors in this volume have discussed the results of the animal reproductive studies. When we first started this study, the only report on effects on humans was done in the Soviet Union on 28 Russian workers (1). The authors reported a reduction in sexual activity. In addition, 6 workers had variable adverse semen quality changes. These were the only human data that were available at the time of our study. The 28 Russian workers were reported by the authors to be exposed to four to eight or more times the maximum permissible concentration (MPC) of boric acid (USSR MPC reported by World Health Organization in 1976 to be 10 mg/m³).

Because of concern that borax and boric acid exposure on the job might reduce worker fertility, we recommended to the company that a questionnaire study be done as the least intrusive and the simplest technique. Still, as described

later in this article, some of the potential participants viewed the study questionnaire as quite invasive.

The strategy of this study was to measure live births as the end point of fertility. While there are many other end points one can measure, this number of offspring is generally well known and not subject to the same recall bias as other outcomes of pregnancy (e.g., spontaneous abortions and birth defects).

Methods

The statistic that we used was the standardized birth ratio (SBR), a summary index employed to determine the rate of fertility (2). In the SBR, live births are compared to the expected numbers. These numbers are derived from U.S. national fertility data for females. Unfortunately, there are no such data either for the state of California or for any of the counties within the state. Therefore, we had to use national data from the U.S. National Center for Health Statistics.

Consequently, our methodology was based on an indirect comparison. To calculate the expected number of births, we used the expected fertility rates of the wives of the male employees; the fertility data on men in the United States is of poor quality. To use data from wives, the wives' age, parity, and race first had to be ascertained. Subsequent direct comparisons within a population then could be made.

The questionnaire information we needed was relatively simple: name or company ID number, date of birth, race, work history, work exposure, marital status, and offspring. Marital history included date of marriage, separation, divorce or widowhood, and date of spouse's birth and number of children from each marriage. Offspring data included the children's sex and dates of birth, and whether they were from a union of the male employee and his wife or were adopted or stepchildren of the men.

To determine the expected number of births a person-year calculation (woman-years at risk) was done. This calculation encompasses the time the woman was at risk of being impregnated by her husband, after his exposure to borax or boric acid. The at-risk period commences 9 months after the husband began working at U.S. Borax. Births that occurred before the normal gestation period were assumed to be preexposure.

Due to the movement of workers in and out of the workforce, not all women contributed equally to the denominator. Additionally, as women age, their fertility rate changes. So maternal ages and parity kept changing.

We held meetings to discuss the study with management and the union leadership. We went to the plant, held a series of informative meetings with all employees regarding the nature and purpose of our study, data confidentiality, and our meth-

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ods of analyzing the data. We requested that all employees participate. We handed out the questionnaires with a letter describing the study and the procedure for returning the completed form.

We described the 2-page questionnaire to the employees. The first page requested the following: name, date of birth, race, marital status, marriages (including dates and separations), children, whether the child was natural, adopted, or a stepchild, and also which marriage resulted in the birth of the child.

The second page included questions about stillbirths and miscarriages (this information is far softer than that based on live birth data). It also included questions about the respondent's medical history, such as: "Have you had a vasectomy?" "Did you have mumps?" "Have you sought medical attention for any fertility problems?" "Have you tried to have children for more than a year and were unable to?" (These are the key questions in assessing whether a couple is infertile or having infertility problems.) In conclusion, we asked, "Is there anything else you want us to know?"

For 3 days following the presentation to employees, we were available at the entrance gates from 6:00 to 7:30 a.m., so employees could give us the completed questionnaires as they came to or left from work. The company did not handle the questionnaires at any point in the process. (We knew employees might have concerns about the company having access to the surveys.) After review of the questionnaires, individuals were called if clarification of their responses was needed.

We asked for assistance since the initial response rate was not as high as desired. The plant manager sent a letter with a copy of the questionnaire to all the management personnel requesting their participation. A stamped envelope expressly addressed to the study team accompanied his letter. With the assistance of the union, a similar letter went to the hourly employees, also with an enclosed self-addressed, stamped envelope.

This effort led to the return of more questionnaires; however, there were still nonparticipants. We then received permission from the company and the union to call the nonparticipants at home. All the telephone surveys were completed by one of our team, Jenifer Haas. All employees were called at home.

After all efforts were exhausted, there were still some nonparticipants. We were concerned that the nonparticipants might have been different from the participants in

a critical way. They could have been nonparticipants because they were upset with the company, because they had no fertility problem, or (we worried) because they had a fertility problem.

The only information source containing the spouse's date of birth and the date of birth of dependents for both participants and nonparticipants was the company medical insurance coverage files. These files were used to make an assessment of the nonparticipants and to evaluate the completeness of the medical insurance coverage files on participants. We took a sample of 10% of the participants and compared their medical insurance coverage files with the completed questionnaires.

All of the work histories were obtained from the personnel department. These data included job titles, departments, and change dates. Exposure information was the same as that reported by Wegman et al. in this symposium. The U.S. Borax industrial hygienist provided exposure classifications by job title over time. Due to the lack of quantification over time, we use three categories: high, medium, or low. Since the industrial hygiene information dated only to 1980, categorization before then required professional judgment. This has been a common issue with other occupational studies.

Results

Demographic

Of the 753 employees, 542 were participants and 211 were nonparticipants. The demographic information for participants and nonparticipants proved to be remarkably similar for race, marital status, and average age. The same was true for length of employment, age at hire, year of birth, and year of hire. We found no significant differences between the two groups.

Standardized Birth Ratio

The summary index for assessing the risk of infertility is the SBR. The number of live births born to the wives of the workers is compared to the number of births that would be expected in the U.S. population adjusted for maternal age, parity, race, and calendar year.

An SBR greater than 100 denotes an excess of births, while less than that shows a deficit. We calculated the SBR by exposure category. The 95% confidence limits were determined for all of the point estimates.

The SBR for the participants was 113, which was both in excess of 100 and statistically significant. Thus, the participants

have had more children than expected. Based on conversations with the employees, this was not a surprising finding since we were repeatedly told, "Why are you doing this study? We are not having a problem with fertility. We have enough kids. We've got a lot of kids."

We calculated separate SBRs, one for a group with low-level exposure and one for a group with medium to high levels of exposure. There was little difference between the categories; both SBRs were in excess of 100.

There was a 36% vasectomy rate among the participants. This rate is similar to two other studies we have done in California in well-paid, blue collar workers (3,4).

Nine percent tried unsuccessfully to conceive for more than a year. Five percent, actually a subset of this 9%, sought help for fertility problems. The national average indicates that about 15% of adult population have some type of infertility problem while 10% of the population have fewer children than they would like.

Gender Ratio in Offspring

Since we obtained data on the sex of the offspring, we also calculated number of male children compared to number of female children. There are data from a dibromochloropropane (DBCP) study that showed men who recovered from testicular effects of DBCP subsequently sired more girls than boys (5). The expected sex rates of births is 51.2% boys and 48.8% girls.

Instead of the expected 48.8% female births, we found 52.7% of the workers' offspring were female. This difference was almost but not quite statistically significant. This increase in number of girls was constant across exposure categories.

This excess of female offspring was not due to a deficit of male offspring. We expected 238 boys and found 249. Thus, there was an excess of 11 boys. Similarly, there was an excess of 51 girls. So it was not a deficit of boys; it was just that there were many more girls.

Participation Issues

The issue of participation needs some discussion. Of the 753 eligible, 542 participated; 211 did not. Of the participants, 426 mailed in their questionnaire while 116 answered the necessary questions in a telephone interview. We addressed the following questions: *a*) Is there a difference among these groups? *b*) Are the participants and nonparticipants similar? *c*) Are the self-administered and telephone administered questionnaire participants similar?

d) How complete are the data obtained from medical insurance coverage files in comparison to the questionnaire data?

For the participants and nonparticipants, we compared their demographic characteristics, the SBRs, and the percentage of female offspring. Our nonparticipant fertility data was limited to medical insurance coverage files.

Previously, we noted that there was a remarkable demographic similarity between the participants and nonparticipants. Based on the medical insurance coverage files, the nonparticipants had an SBR of 92. This is not a statistically significant deficit. The summation of the SBR for the participants and nonparticipants was 108, a statistically significant excess. The SBRs across exposure categories for the nonparticipants, as before, did not show any trend.

The percentage of female offspring showed the participants and nonparticipants to be almost identical at 52.7 and 51.6%, respectively. Once again, there were no differences based on the exposure levels.

Next we assessed the participants by method of completion of the questionnaire: 116 telephone-administered and 426 self-administered. The demographic data were very similar for age of hire, year of birth, year of hire, and age. The self-administered group was employed, on average, 1.5 years longer than the telephone-administered group.

The telephone-administered group had a slightly higher vasectomy rate, but there was no difference regarding fertility difficulties. The telephone-administered group's SBR was slightly higher than the self-administered group. The same results are present by the exposure categories.

The telephone-administered group percent female offspring was about 3% lower than the self-administered group percent female offspring; this percentage was still higher than expected. The telephone-administered group appears not to have had a fertility problem, which may be the reason why they did not initially respond.

As discussed earlier, we evaluated the medical insurance coverage file. We took a random sample of 10% of those who completed the questionnaire. In addition, we abstracted information in these records for family demographic information.

In the 10% sample, the SBRs were slightly higher for the questionnaire responses, compared to the respective medical insurance coverage file. The percentage female offspring was greater

(4.5%) in the medical insurance coverage file compared to the questionnaires.

The medical insurance coverage files proved that the questionnaires were effective in identifying births. These files also were shown to be a useful screening procedure to determine if the nonparticipants had a different pattern of fertility from the participants.

In summary, we did not see any meaningful differences between the participants and nonparticipants, the self-administered versus the telephone-administered questionnaire groups, or the medical insurance coverage records and the 10% sample of the questionnaire participants. We believe that the nonparticipants did not skew our results.

Exposure Issues

We also examined the fertility rates of individuals who were in a high-exposure category job for 2 years or more, (i.e., people in the long-term, high-exposure category). The summary SBR for this group was 88, with 33 observed births and 37 expected.

We next examined the length of time after beginning and cessation of high exposure. We looked at those individuals who had been in the high-exposure categories for 2 years or more and tracked them from the time 12 months after they started the job to 12 months after they left the job. We did the same process for 15 months and 18 months.

Twelve months would allow the man to have one spermatogenic cycle prior to a pregnancy. Fifteen months is two spermatogenic cycles, while 18 months is three cycles. If there were an adverse fertility effect, one should be able to detect it in this manner. The respective SBRs for 12, 15, and 18 months were 121, 123, and 125.

Other Issues

Another issue to examine was the effect of the protracted strike in 1973 to 1974. We could determine if the excess of children (fertility) could be related to a prolonged period of unemployment. The SBR for pregnancies occurring during the strike was 136; however, they represented only 17 births out of the total of 529. Thus, the higher SBR occurring during the strike is not the reason for the overall increased SBR. The percent female offspring rose during the strike and never returned to the prestrike average.

We evaluated the SBRs and percent female offspring by 5-year time periods

from 1950 to 1990. In every 5 year grouping, the SBR is greater than 100. The SBR for 1980 to 1984 was statistically significant at 128. Similarly, just during the 1980s there were fewer girls born than expected.

One hypothesis for the greater incidence of children than expected is that fathers wanted a son but only were having daughters. Their families grew larger and larger as they kept trying for a son. If this were so, then one should see families with many girls and one son. An examination of the size of families by gender of their children does not support this hypothesis. The gender ratio of the families, in general, does not explain the excess of girls.

Study Strengths and Weaknesses

This study has the following strengths: a noninvasive methodology, sufficient statistical power, adequate assessment of the nonparticipants, no demonstrable bias, and births used as the measure of fertility.

The weaknesses of the study include: questionnaire response lower than optimal; historical exposure categorizations based on incomplete data; and failure of the methodology to measure direct effect on the gonads. If borate exposure has a subtle effect on semen parameters, this method of fertility assessment may not detect it.

Summary

In summary, our study provided a good ascertainment of live births. There is no evidence of selection bias. The SBRs were consistently elevated. There was no adverse effect that could be connected to either borate exposure or temporal events. Increase in percentage of female offspring has been consistent for the past 20 plus years and does not appear to be related to borate exposure. We have no explanation for this, either the increase in fertility as measured by the SBRs, or the increase in the percentage of female offspring.

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